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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,930	04/12/2004	Dario Neri	ELLIS-0002-P02-C01	3681

23599 7590 01/04/2010

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
2200 CLARENDON BLVD.
SUITE 1400
ARLINGTON, VA 22201

EXAMINER	
PORTNER, VIRGINIA ALLEN	
ART UNIT	PAPER NUMBER
1645	

NOTIFICATION DATE	DELIVERY MODE
01/04/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

docketing@mwzb.com

Office Action Summary	Application No.	Applicant(s)	
	10/821,930	NERI ET AL.	
	Examiner	Art Unit	
	GINNY PORTNER	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-26,28-34 and 36-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *19-26,28-34 and 36-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *29 September 2009* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/29/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 19-26,28-34,36-45 are pending.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on September 29, 2009 has been entered.

Information Disclosure Statement

1. The information disclosure statement filed September 29, 2009 has been considered.

2. The information disclosure statement filed February 8, 2005, reference 94 does not set forth a date for the reference, thus the citation is incomplete.

Drawings

3. The drawings (Figure 6) is objected to under 37 CFR 1.83(a) because it fails to show SEQ ID NO 20 and 21 as described in the specification. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet,

even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

- Figure 6, in the amendment dated September 4, 2007 was described in the Brief description of the drawings to comprise SEQ ID NO 19 (VH), SEQ ID NO 20 (14 mer linker) and SEQ ID No 21 (VH).

At page 14, line 2 of the specification, please amend as follows:

Fig. 6 shows amino acid sequence of L19 (VH, linker and VL, SEQ ID NOS: 19-21, respectively);

- Figure 6 submitted in the amendment dated September 29, 2009 deleted the sequences for SEQ ID NO 20 and 21 from Figure 6. The Brief Description of the Drawings now describes details that are not shown in the present Figure 6.

Sequence listing

4. The current sequence listing in the instant Application was incorporated based upon Applicant's letter requesting the transfer of the sequence data from parent application 09/512,082 dated April 12, 2004.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

Dario NERI et al.

Serial No.: Examiner: Victoria A. PORTNER

Filed: April 12, 2004 Group Art Unit: 1645

For: SPECIFIC BINDING MOLECULES FOR SCINTIGRAPHY, CONJUGATES CONTAINING THEM AND THERAPEUTIC METHOD FOR TREATMENT OF ANGIOGENESIS

REQUEST FOR TRANSFER OF CRF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The paper copy of the Sequence Listing for this application, is identical to the computer readable copy of the Sequence Listing filed in application, 09/512,082 on February 24, 2000. In accordance with 37 CFR 1.821(e), please use the last-filed computer-readable form filed in that application as the computer readable form for the instant application. It is understood that the Patent and Trademark Office will make the necessary change in application number and filing date for the instant application. A paper copy of the Sequence Listing is included in a separately filed amendment, for incorporation into the specification.

Respectfully submitted,

Anthony J. Zelano, Reg. No. 27,969
Attorney for Applicants

MILLEN, WHITE, ZELANO & BRANIGAN, P.C.
Arlington Courthouse Plaza I
2200 Clarendon, Suite 1400
Arlington, VA 22201
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Facsimile: (703) 243-6410

Attorney Docket No.: ELLIS-2-P3

Filed: April 12, 2004
K:\Ellis-2\P3\ReqTransfer.doc

5. Applicant's subsequent request to transfer the computer readable form (CRF) sequence listing from 09/300,425 was received 9/4/2007, but not incorporated because the rules for transfer and incorporation of a sequence listing from a grand-parent application were not met.

IN THE UNITED STATES PATENT AND TRADEMARK C

In re Application of:

Dario NERI et al. Examiner: Virginia Alh

Serial No.: 10/821,930 Group Art Unit: 1645

Filed: April 12, 2004

Title: SPECIFIC BINDING MOLECULES FOR SCINTIGRAPHY, CONJUGATES CON THEM AND THERAPEUTIC METHOD FOR TREATMENT OF ANGIOGENES

REQUEST TO TRANSFER CRF

Mail Stop
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The paper copy of the Sequence Listing for this application (10/821,9 the computer readable copy of the Sequence Listing filed in application, 09/3 22, 2000. In accordance with 37 CFR 1.821(e), please use the last-filed com filed in that application as the computer readable form for the instant applica understood that the Patent and Trademark Office will make the necessary ch number and filing date for the instant application. A paper copy of the Sequ included in a separately filed amendment, for incorporation into the specific

Respectfully submitted,

/Anthony J. Zelano/
Anthony J. Zelano, Reg. No. 27

6. The paper copy of the sequence listing submitted 9/4/2007 is present in the file of the instant application and sets forth, two sequences that have been deleted from originally filed Figure 6, and from the claims. The isolated antibody of the instant claims evidences an amino acid sequence that differs from originally filed sequences SEQ ID NO 20 and SEQ ID NO 21, which were the sequence providing original descriptive support for the linker and the VL chain of antibody L19. see immediately below:

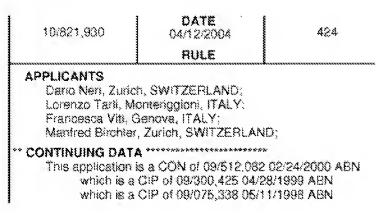
```
<210> SEQ ID NO 20
<211> LENGTH: 14
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: antibody
linker
<400> SEQUENCE: 20
      Gly Asp Gly Ser Ser Gly Gly Ser Gly Gly Ala Ser Thr Gly
        1               5                  10

<210> SEQ ID NO 21
<211> LENGTH: 108
<212> TYPE: PRT
<213> ORGANISM: Artificial Sequence
<220> FEATURE:
<223> OTHER INFORMATION: Description of Artificial Sequence: VL antibody
      specific for ED-B domain of fibronectin
<400> SEQUENCE: 21
      Glu Ile Val Leu Thr Gln Ser Pro Gly Thr Leu Ser Leu Ser Pro Gly
       1               5                  10                  15
      Glu Arg Ala Thr Leu Ser Cys Arg Ala Ser Gln Ser Val Ser Ser Ser
                  20                  25                  30
      Tyr Leu Ala Trp Tyr Gln Gln Lys Pro Gly Gln Ala Pro Arg Leu Leu
              35                  40                  45
      Ile Tyr Tyr Ala Ser Ser Arg Ala Thr Gly Ile Pro Asp Arg Phe Ser
          50                  55                  60
      Gly Ser Gly Ser Gly Thr Asp Phe Thr Leu Thr Ile Ser Arg Leu Glu
      65                  70                  75                  80
      Pro Glu Asp Phe Ala Val Tyr Tyr Cys Gln Gln Thr Gly Arg Ile Pro
                      85                  90                  95
      Pro Thr Phe Gly Gln Gly Thr Lys Val Glu Ile Lys
                  100                 105
```

7. The sequences in the Application are inconsistent with the originally filed sequence listing in light of the fact that the claims recite a Deposited clone that evidences an amino acid sequence for antibody L19 that is other than that originally present in the parent applications and

the instant sequence listing, the instant sequence listing having been transferred into the instant Application from the parent application.

Priority

8. The instant Application serial number is ***10/821, 930*** and claims priority to applications ***09/512,082, 09/300,425 and 09/075,338*** and does Not claim priority to US Patent Application ***10/321, 558.***


10/821,930 | DATE 04/12/2004 | 424
RULE

APPLICANTS
Dario Neri, Zurich, SWITZERLAND;
Lorenzo Tarli, Monteriggioni, ITALY;
Francesca Viti, Genova, ITALY;
Manfred Birchler, Zurich, SWITZERLAND;

** CONTINUING DATA **********
This application is a CON of 09/512,082 02/24/2000 ABN
which is a CIP of 09/300,425 04/28/1999 ABN
which is a CIP of 09/075,338 05/11/1998 ABN

9. Applicant's response dated September 29, 2009 refers to application 10/321, 558 and the issues raised in that Application. Application's remarks are directed to a different Application and not the instant Application 10/821,930. The instant Application does not contain any official declarative evidence submitted under 37 CFR 1.132. The instant Application file history does not contain a Lundak Declaration. Remarks directed to issues raised in 10/321,558 relative to a Declaration that has not been filed in the instant Application are out of context and inconsistent the file history of the instant Application. In so far as Applicant's remarks relate to specific issues in the instant Application, the examiner will respond.

Response to Amendment

1. In response to the objection and rejection to the amendment filed March 10, 2009 objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: **Specification and Claims:** "DNA encoding antibody scFv L-19 has been deposited on September 25, 2008, in ATCC (Manassas, VA) and has accession number PTA-9529." The DNA deposited does not evidence original descriptive support in the instant Specification at the time of filing. The original sequence listing and original Figure 6 provided the amino acid sequence for the L-19 antibody, but Applicant states that the sequence encoded by the deposited DNA encodes a different amino acid sequence from that disclosed in Figure 6, as originally filed. **Specification**: The paragraph amendments at page 22 and 23 which change the positions for randomization from positions 32 and 50 to positions 33 and 50 do not evidence original descriptive support in the instant Specification, and is therefore New Matter. While Applicant changed back the mutation location to position 32 on page 22, Applicant's amendment did not change back the mutation location to position 32 on page 23; which still recites position 33. The Specification still contains New Matter in light of the amendment of the Specification submitted on March 10, 2009 of page 23, line 3 which changed the location from position 32 to position 33.

2. The specific linker disclosed in the instant Specification (SEQ ID NO 20, 14 amino acids), is not the linker of the Deposited DNA which lacks the last two amino acids "TG". No linkers of 12 amino acids in length evidence original descriptive support in the instant Specification (see original Figure 6, for amino acid sequence for the Linker has 14 amino acids).

VH

EVQLLESGGG LVQPGGSLRL SCAASGFTFS
SFSMSWVRQA PGKGLEWVSS ISGSSGTTYY
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED
TAVYYCAKPF PYFDYWGQGT LVTVSS

linker

GDGS3GGS5GGASTG

VL

EIVLTQSPGT LSLSPGERAT LSCRASQSVS
SSYLAWYQQK PGQAPRLLIY YASSRATGIP
DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ
QTGRIPPTFG QGTKVEIK

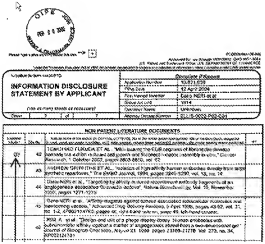
Figure 6: Amino acid sequence of antibody L19

3. Both the amendment of the Specification and the newly submitted claims recite the ATCC deposit no. PTA-9529 which comprises a linker of 12 amino acids, and a different amino acid sequence for the VL chain, as well as a DNA coding sequence that did not evidence original descriptive support at the time of filing of the instant Specification all of which is considered to be New Matter as these changes do not evidence original descriptive support in the instant Application.

- Applicant traverses the objection to the Specification and rejection of the claims for reciting New Matter by asserting the sequence errors were "inadvertent errors in reporting the sequence of L19 to the public".
- States that the sequence in Pini et al (August 1998, reference filed on Applicant's USPTO-1449) that refers to an EBI database deposit containing the sequence for L19 contained the same error in identifying the linker as having 14 amino acids and this sequence has been changed to be a 12 mer linker which is consistent with the linker in the claimed Deposited antibody.

4. It is the position of the examiner that no evidence has been made of record in the instant Application relative to the controlling decisions for making changes to sequence disclosures to show inadvertent sequencing errors. Applicant is directed to consider the controlling decision in 27 USPQ2d 1662 Ex parte Maizel U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences No. 91-2301 Decided May 27, 1992 On Reconsideration October 19, 1992, with respect to changing sequences for antibody L19 within this application.

5. Upon consideration of Applicant's statements, the email history submitted as Exhibit 2 to which was attached the sequence listing from 1998 for EBI AJ006113, the EBI AJ006113 sequence being associated with the Pini et al reference that describes the antibody L19, it was noted by the examiner that EBI AJ006113 contained a 14 mer linker encoded by the DNA sequence as of November 1998, which is after the claimed priority date for the instant Application, and this sequence had been updated from the originally submitted sequence that had been filed in May 1998.



OIPE FEB 0 8 2006 PATENT & TRADEMARK OFFICE

Substitute for form 1449/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(Use as many sheets as necessary)

Sheet 2 of 7

Complete if Known	
Application Number	10/821,930
Filing Date	12 April 2004
First Named Inventor	Dario NERI et al
Group Art Unit	1614
Examiner Name	Unknown
Attorney Docket Number	[illegible]

NON PATENT LITERATURE DOCUMENTS

Examiner Initials	Cite No.		
[illegible]	42	TOMOHIKO FUKUDA ET AL., "[illegible] the EDB segment of fibronectin [illegible] cell growth and fibronectin matrix assembly in vitro," Cancer Research, 1 October 2002, pages 5603-5610, vol. 62	
	43	ANDREW GRIFFITHS ET AL., "Isolation of high affinity human antibodies directly from large synthetic repertoires," The EMBO Journal, 1994, pages 3245-3260, vol. 13, no. 14	
	44	Dario NERI et al., "Targeting by affinity-matured recombinant antibody fragments of an angiogenesis associated fibronectin isoform", Nature Biotechnology, Vol. 15, November 1997, pages 1271-1275	
	45	Dario NERI et al., "Affinity reagents against tumour-associated extracellular molecules and newforming vessels," Advanced Drug Delivery Reviews, 6 April 1998, pages 43-52, vol. 31, no. 1-2, XP002124780, pages 46, right-hand column, page 49, left-hand column.	
	46	PINI A. et al., "Design and use of a phage display library. Human antibodies with subnanomolar affinity against a marker of angiogenesis eluted from a two-dimensional gel," Journal of Biological Chemistry, August 21 1998, pages 21769-21776, Vol. 273, no. 34, XP002124781	

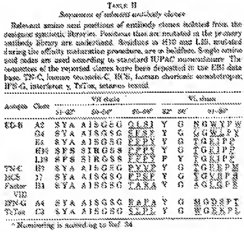


TABLE II
Sequences of selected antibody clones

Relevant amino acid positions of antibody clones isolated from the designed synthetic libraries. Positions that are mutated in the primary antibody library are underlined. Residues in H10 and L19, mutated during the affinity maturation procedure, are in boldface. Single amino acid codes are used according to standard IUPAC nomenclature. The sequences of the reported clones have been deposited in the EBI data base. TN-C, human tenascin-C; HCG, human chorionic gonadotropin; IFN-G, interferon γ; TeTox, tetanus toxoid.

Antigen	Clone	VH chain 31-33[a]	VH chain 50-56[a]	VH chain 95-98[a]	VL chain 32[a]	VL chain 50[a]	VL chain 91-96[a]
ED-B	A2	S Y A	A I S G S G	Q L A I	Y	G	N G W Y P W
	G4	S Y A	A I S G S G	E E S F	Y	G	G G W L P Y
	E5	S Y A	A I S G S G	E E P Y	Y	G	T G R I P P
	H10	S F S	S I R G S S	F F P Y	Y	G	T G R I P P
	L19	S F S	S I R G S S	F F P Y	F	Y	T G R I P P
TN-C	B7	S Y A	A I S G S G	P Y Y P	Y	G	T G R R P M
HCG	37	S Y A	A I S G S G	P P R F	Y	G	T G Y R P H
Factor VIII	B1	S Y A	A I S G S G	T A K A	Y	G	A G L G P R
IFN-G	A4	S Y A	A I S G S G	R A P A	Y	G	M G D S P T
TeTox	C3	S Y A	A I S G S G	S Y P L	Y	G	W G E K P L

[a] Numbering is according to Ref. 34.

Additionally, the examiner went to Swiss-Prot to find the amino acid sequence for the linker for L19. The amino acid sequence for the L19 antibody(VH and VL chains) and linker was made public through Swiss-Prot, and the scFv antibody L19 was described in the Journal of Biological Chemistry article to Pini et al. 1998 (Reference cited on Applicant's USPTO 1449). The L19 antibody disclosed by Pini et al comprised an amino acid sequence linker (see Table II, page 21772 of Pini et al) inserted between the VH and VL chains which is 14 amino acids in length, and ends in amino acids "TG" (see Swiss-Prot accession numbers A2KBC0, A2KBC1, A2KBC2, A2KBC3, A2KBC4, A2KBC5, A2KBC6, A2KBC7, A2KBC8, A2KBC9, publically available information (accession numbers for all ED-B antigen antibodies shown in Table II, of Pini et al, one of which is L19).

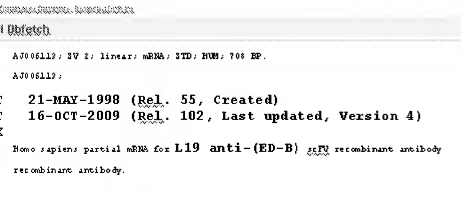
Independent claim 1 is broad enough to read on the VH and VL domains (Swiss-Prot A2KBC1)

6. Upon consideration of the EMBL EBI AJ006113 sequence and the Swiss-Prot amino acid sequence for antibody L19, and the linker contained therein, it was noted that the linker sequence was changed by one of the named inventors, Viti , in October 2009 and November 2009, respectively: provided immediately below:

EBI AJ006113

EBI Dbfetch

```
ID   AJ006113; SV 2; linear; mRNA; STD; HUM; 708 BP.
XX
AC   AJ006113;
XX
DT   21-MAY-1998 (Rel. 55, Created)
DT   16-OCT-2009 (Rel. 102, Last updated, Version 4)
XX
DE   Homo sapiens partial mRNA for L19 anti-(ED-B) scFv recombinant antibody
XX
KW   recombinant antibody.
XX
```



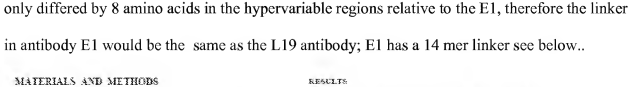
Swiss-Prot L19 Data November 2009

A2KBC1-1 [UniParc]. FASTA

Last modified **November 24, 2009.**
Version 2.
Checksum: 44BFD9D23B9070E5

```
        10          20          30          40
50          60
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SFSMSWVRQA
PGKGLEWVSS ISGSSGTTYY

        70          80          90          100
110         120
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKPF
PYFDYWGQGT LVTVSSGDGS

       130         140         150         160
170         180
SGGSGGASEI VLTQSPGTLS LSPGERATLS
CRASQSVSSS FLAWYQQKPG QAPRLLIYYA

       190         200         210         220
230
SSRATGIPDR FSGSGSGTDF TLTISRLEPE DFAVYYCQQT
GRIPPTFGQG TKVEIK
```

7. Upon further consideration of the antibody L19, the examiner found Inventor Viti et al 's statements in Cancer Research 1999, pages 347-348, in which he states that the L19 antibody only differed by 8 amino acids in the hypervariable regions relative to the E1, therefore the linker in antibody E1 would be the same as the L19 antibody; E1 has a 14 mer linker see below..



MATERIALS AND METHODS

Production of Anti-ED-B Affinity Mutants. The isolation of the E1 and L19 Abs has been described previously (18). E1 is a scFv binding to the ED-B domain of fibronectin that is isolated from a synthetic human phage display Ab library. L19, a mutant of E1 with 760-fold improved affinity, differs from the parental Ab by eight mutations introduced in [redacted] loops (European Molecular Biology Laboratory accession no. AJ006113; Ref. 18)

RESULTS

Ab Fragment. We have recently characterized (18) the isolation of two human scFv Ab fragments, E1 and L19, with picomolar, comparable affinity for the ED-B domain of fibronectin of 41 and 2.0 pM, respectively. L19 is an affinity-matured version of E1, obtained by combinatorial mutagenesis of preliminarily selected residues in the hypervariable loops of E1 and selected using phage display technology (18, 19). The enhanced binding affinity of L19 is mainly due to a lower kinetic dissociation constant (18). Immunohistochemistry studies with tumor sections have demonstrated that both Abs recognize ED-B-containing fibronectin in vascular structures (18)

The amino acid sequences for all of the linkers in the ED-B antibodies of Pini et al 1998, E1 along with L19 are shown in Table 2, have 14 mer linkers in them, which are discussed in Viti et al 1999. see below:

A2KBB9-1 [UniParc]. FASTA 238 25,145 Blast go

Last modified February 20, 2007. Version 1. Checksum: 7875A9A25E4ED418

```
        10         20         30         40         50
60
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSA
ISGSGGSTYY

        70         80         90        100        110
120
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKPF PYFDYWGQGT
LVTVSSGDGS

          130        140        150
160        170        180

SGGSGGASTG EIVLTQSPGT LSLSPGERAT LSCRASQSVS
SSYLAWYQQK PGQAPRLLIY

       190        200        210        220        230
GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QTGRIPPTFG
QGTKVEIK
```

A2KBC2-1 [UniParc]. FASTA 238 25,193 PeptideCutter go

Last modified February 20, 2007. Version 1.

Checksum:
D1ACADF21EBA1F1A

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          10          20          30
40          50          60
EVQLLESGGG LVQPGGSLRL SCAASGFTFS
SYAMSWVRQA PGKGLEWVSA ISGSGGSTYY

          70          80          90
100         110         120
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED
TAVYYCAKGL SIFDYWGQGT
LVTVSSGDGS

          130         140
150         160
170         180
SGGSGGASTG EIVLTQSPGT
LSLSPGERAT LSCRASQSVS SSYLAWYQQK
PGQAPRLLIY

          190         200         210
220         230
GASSRATGIP DRFSGSGSGT DFTLTISRLE
PEDFAVYYCQ QNGWYPWTFG QGTKVEIK
```

A2KBC0-1 [UniParc].	FASTA	238	25,205	Blast go

Last modified
February 20, 2007.
Version 1.
Checksum:
E460C9C44AF1D558

```
          10          20          30          40          50
```

60
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SFSMSWVRQA PGKGLEWVSS
ISGSSGTTYY

70 80 90 100 110
120
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKPF PYFDYWGQGT
LVTVSS**GDGS**

130 140 150
160 170 180
SGGSGGASTG EIVLTQSPGT LSLSPGERAT LSCRASQSVS
SSYLAWYQQK PGQAPRLLIY

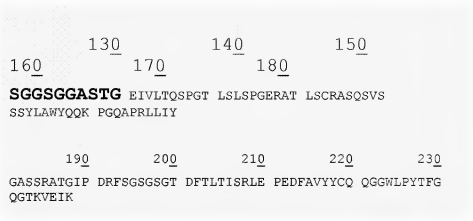
190 200 210 220 230
GASSRATGIP DRFSGSGSGT DFTLTISRLE PEDFAVYYCQ QTGRIPPTFG
QGTKVEIK

A2KBC3-1 [UniParc]. FASTA 238 25,161 Blast go

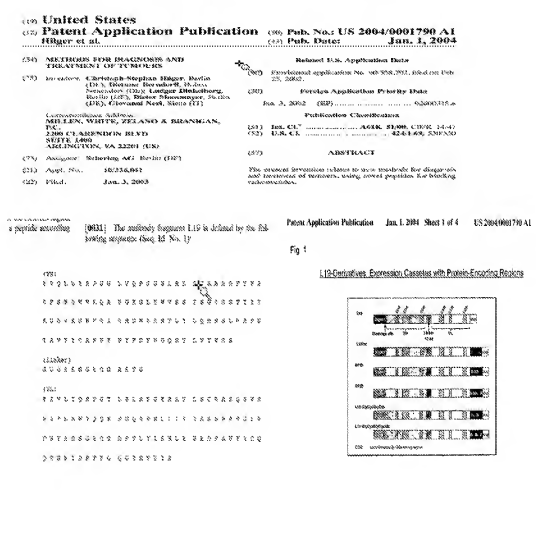
Last modified February 20, 2007. Version 1. Checksum: D4F33E085ED956E9

10 20 30 40 50
60
EVQLLESGGG LVQPGGSLRL SCAASGFTFS SYAMSWVRQA PGKGLEWVSA
ISGSGGSTYY

70 80 90 100 110
120
ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYYCAKSF SFFDYWGQGT
LVTVSS**GDGS**



8. The examiner found additional disclosure supporting the fact that antibody L19 contains a 14 mer amino acid linker supported by US PG-Pub 2004/0001790.



9. In conclusion, the New Matter objection to the Specification and rejection of the claims made of record in the prior office action, for reciting sequences that do not evidence original descriptive support in the instant Specification as originally filed is maintained for reasons of record and responses set forth herein.

Claim Rejections - 35 USC § 112

10. Claims 19-26,28-34, 36-45 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is traversed on the grounds that the Neri Lundak Declaration is fully sufficient to support the current claims.

11. It is the position of the examiner that the referenced Lundak Declaration has not been filed in the instant Application; Applicant's traversal and grounds of traversal are insufficient to overcome the New Matter rejections of record.

12. Claims 19-26, 28-34 all claim an antibody or methods of administering an antibody that is encoded by a DNA coding sequence that did not evidence original descriptive support at the time of filing of the instant Specification. Upon consideration of Example 2, the examiner found the example to generate 4 X 18^{8} clones, of which 25 % were positive. The amino acid sequence for L19 is shown in original Figure 6. No other sequences for L19 have been described or disclosed. The Deposited DNA perports to encodes an amino acid sequence other than that described in the instant Specification for L19, for both the linker and the VL chain; the recitation of this coding DNA based upon a Deposit that was not set forth in the original Specification and is described as encoding amino acid sequences other than what the instant Specification provides original descriptive support, intorduces New Matter into the amended claims and Specification.

13. Claims 36-45 all claim an antibody that comprises a linker encoded by DNA of the Deposit ATCC No. PTA-9529. The linker of the newly submitted claims does not evidence original support in the instant Specification which discloses a linker of 14 amino acids, SEQ ID No 31, and not a linker lacking the last two amino acids "TG". All of the claims recite a species

of linker that does not evidence original descriptive support in the instant Specification or the original claims. Claims 36-45 recite New Matter.

14. In response to the examiner's New Matter rejection of Claim 28 which was amended to recite a conjugate that comprises a molecule that is both a "photosensitizer and a molecule which is a radionuclide", Applicant points to original claim 28 for support for what is now claimed.

15. Upon reconsideration of original claim 28, and claim 33 which depends directly from original claim 28, the examiner found claim 33 to only recites a single type of label molecule rather than a combination molecule as asserted by Applicant's representative.

16. Additionally original claims 24 and 27 each set forth molecules that are only one type of label, and not the combination label as now claimed in claim 28. Therefore instant claim 28 does not find original descriptive support in original claim 28 which set forth a type of species listing (Markush) rather than a molecule with both characteristics of being a photosensitizer and a radionuclide at the same time.

17. No original descriptive support for a molecule that has both characteristics could not be found in the instant Specification. Tin chlorin e6 is a photosensitizer, but not a radionuclide and a Beta emitter is a radionuclide, but is not a photosensitizer. Therefore the amendment of claim 28 introduces a new subgenus of species of conjugate that does not evidence original descriptive support in the instant Specification. The rejection of record is maintained for reasons of record and responses set forth herein.

Claim Objections

18. The objection to claim 24 because of the following informalities was not resolved by Applicant's claim amendment as claim 24 still recites the term "chlorine", but should be amended to recite----- chlorin-----. . The objection is maintained for reasons of record. Appropriate correction is required.

New grounds of Rejection

Claim Rejections - 35 USC § 102

19. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (f) he did not himself invent the subject matter sought to be patented.
>
> (g)(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other.

20. Claim 19, 20, 36 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter. US Patent which does not share a common inventor or common assignee claims a conjugate of a recombinant monoclonal antibody fragment (claims 1, 14) that is specific for the ED-B domain of fibronectin (claim 9) and a method of treating a tumor (allowed claim 15), wherein the only recombinant antibody fragment that binds to the ED-B domain of fibronectin disclosed in US Patent 7,129,254 is referred to as SEQ ID NO 1 and shares 100% identity with the instantly claimed antibody conjugate and method of treating a tumor.

Variable Heavy Chain

```
Qy          1 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFSMSWVRQAPGKGLEWVSSISGSSGTTYY 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 EVQLLESGGGLVQPGGSLRLSCAASGFTFSSFSMSWVRQAPGKGLEWVSSISGSSGTTYY 60

Qy         61 ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPFPYFDYWGQGTLVTVSS 116
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 ADSVKGRFTISRDNSKNTLYLQMNSLRAEDTAVYYCAKPFPYFDYWGQGTLVTVSS 116


          Qy          1 GDGSSGGSGGAS 12
                        ||||||||||||
linker    Db        117 GDGSSGGSGGAS 128
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Variable light chain (below)

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Qy          1 EIVLTQSPGTLSLSPGERATLSCRASQSVSSSYLAWYQQKPGQAPRLLIYYASSRATGIP 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        129 EIVLTQSPGTLSLSPGERATLSCRASQSVSSSFLAWYQQKPGQAPRLLIYYASSRATGIP 188

Qy         61 DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQTGRIPTFGQGTKVEIK 108
              ||||||||||||||||||||||||||||||||||||||||||||||||
Db        189 DRFSGSGSGTDFTLTISRLEPEDFAVYYCQQTGRIPPTFGQGTKVEIK 236
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The Deposited DNA recited in the claims changes the sequence of the VL sequence of L19 to be "SFLA" instead of SYLA, which is the Db sequence of US Pat. 7,129,254, SEQ ID NO 1.

21. Claims 19-20, 36,39-42, 44-45 rejected under 35 U.S.C. 102(g) based upon claims 1, 9 and 14 of Patent No. 7,129,254. Failure to present claims and/or take necessary steps for interference purposes after notification that interfering subject matter is claimed constitutes a disclaimer of the subject matter. This amounts to a concession that, as a matter of law, the patentee is the first inventor in this country. See *In re Oguie*, 517 F.2d 1382, 186 USPQ 227 (CCPA 1975).

Double Patenting

22. A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

23. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

24. Claims 20-26,28,36,37-45 provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 42-49, 59 and 61 of copending Application No. 10/321,558. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

25. Claims 20-26,28,36-45 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13 of copending Application No. 10/336,041. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application claims encompasses the instantly claimed invention, the instant claims being a species (L19 claimed in 10/336,041)

within the claimed genus of 10/336,041. A common inventor shared between the two applications, specifically Inventor Giovanni Neri. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

26. Applicant is requested to make of record a listing of any additional applications that are claiming the subject matter of the instant Application.

Conclusion

27. This is a non-final action.

28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to GINNY PORTNER whose telephone number is (571)272-0862. The examiner can normally be reached on flextime, but usually M-F, alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert Mondesi can be reached on 571-272-0956. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ginny Portner/
Examiner, Art Unit 1645
December 10, 2009

/Robert B Mondesi/
Supervisory Patent Examiner, Art Unit 1645